UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,390	12/31/2003	Nicholas V. Perricone	01961-P0209B	8977

24126 7590 08/20/2008

ST. ONGE STEWARD JOHNSTON & REENS, LLC
986 BEDFORD STREET
STAMFORD, CT 06905-5619

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
08/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/750,390	PERRICONE ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 11-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8 and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 7, 9 and 10 have been cancelled. Claims 1-6, 8 and 11-16 are under examination.

Withdrawn rejections:

Applicant's amendments and arguments filed 5/7/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8 and 11-16 remain/are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of "non-liposome multilamellar crystal non-polar phosphatidylcholine " was not described in the specification as filed, and person skilled in the art would not recognize in the applicant's disclosure a description of the invention as presently claimed. The specification discloses that topical delivery compositions are non-polar in [0010] but not that the phosphatidylcholine is non-polar and that the topical drug delivery compositions may be in liquid crystal phase but not crystal phase [0014]. The Examiner cannot envision how phosphatidylcholine could be non-polar because it is a charged molecule. The Examiner cannot

find a reference to "non-liposome' either. Therefore, it is the Examiner's position that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of filing of the instant application.

Response to arguments:

Applicant asserts that the Examiner has misunderstood instant claim 1 and the proper reading of claim 1 is that the carrier superstructure as a whole is non-polar. The Examiner looked to the specification to see what is meant by "carrier superstructure". In claim 2, a method of preparing the formulation comprises combining ***polar*** polyglycol of MW 200 and ***polar*** polyglycol of MW 400 to form a ***polar*** polyglycol mixture and then ***polar*** phosphatidylcholine is shaved into the ***polar*** polyglycol mixture to form a ***polar*** phosphatidylcholine solution and the ***polar*** solution is mixed until the ***polar*** solution is clear. Applicant's arguments are not persuasive because the carrier is ***polar***.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8 and 11-16 remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "non-polar carrier". It is unclear to the Examiner how the carrier can be non-polar if it contains multilamellar *polar*

phosphatidylcholine. Claims 2-13 are rejected as being indefinite because they are dependent on an indefinite base claim.

Response to arguments:

Applicant asserts that the Examiner has misunderstood instant claim 1 which recites "non-polar carrier". Respectfully, the Examiner cannot agree. In claim 2, a method of preparing the formulation comprises combining ***polar*** polyglycol of MW 200 and ***polar*** polyglycol of MW 400 to form a ***polar*** polyglycol mixture and then ***polar*** phosphatidylcholine is shaved into the ***polar*** polyglycol mixture to form a ***polar*** phosphatidylcholine solution and the ***polar*** solution is mixed until the ***polar*** solution is clear. Applicant's arguments are not persuasive because the carrier is ***polar***.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6, 8 and 11-16 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Amselen et al. (U.S. Patent No. 5,662,932) or Lynch et al. (US 2002/0153509) in view of Hansen et al. (4,614,730) and Patel et al. (U.S. Patent No. 6,294,192) and, with respect to claims 2-6, 8, 15 and 16, Chaiyawat et al. (US 6,538,061) and Brieva et al. (US 5,985,298).

Applicant claims a method of formulating an insulin composition comprising preparing a carrier having a non-liposome multilamellar liquid crystal phosphatidylcholine non-polar carrier.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Amselen et al. teach a method of making a nanoemulsion for administration of a drug comprising preparing a mixture comprising phospholipid and triglyceride (column 14, lines 22-67 and Claim 27). Amselen et al. teach that the core of the particles is solid or liquid crystalline rather than an oil in a fluid phase and can encapsulate medicaments (column 2, lines 43-54). Amselen et al. teach that the phospholipid can be soy lecithin (phosphotidylcholine) and may be saturated or unsaturated and comprise at least 50% of the total phospholipids (column 6, line 65 through column 7, line 52). (Please note that soy lecithin is enriched with polyenylphosphatidylcholine). Amselen et al. teach that rigid bilayer envelopes are expected thus reading on multilamellar (column 6, lines 56-57 and column 7, lines 39-41). Amselen et al. teach

adding nonnatural surfactants such as Tween, SDS and NP-40 (nonylphenylpolyethylene glycol) as well as numerous other synthetic molecules comprise less than 10% (mol/mol) of the total surfactant (Column 7, lines 54-67). Amselen et al. teach that proteins and peptides such as insulin may be present (column 6, lines 21-25). Amselen et al. teach topical administration of the preparation (claim 34). Amselen et al. teach using a homogenizer to mill the composition to ultimately form stable formulations (Column 15, example 1, for example). Amselen et al. teach hydrating the drug-lipid mixture with the aqueous phase utilizing mechanical shaking and homogenizing the resultant dispersion (column 8, lines 58-66 and column 23, example 22, for example). Amselen et al. do not expressly teach that the carrier is non-polar but since the components are the same as instantly claimed, then it is the Examiner's position that it would be non-polar in the absence of evidence to the contrary.

Lynch et al. teach a method of preparing a cubic liquid crystalline active ingredient carrier in claims 17-20. Claim 17 is partially reproduced below:

> phase.
>
> 17. A method for preparing the cubic liquid crystalline phase precursor of claim 1 comprising the steps of: combining (A) an amphiphile capable of forming a cubic liquid crystalline phase, (B) an optional solvent, (C) an additive selected from the group consisting of an anchor, a tether, and combinations thereof, and (D) an active ingredient, wherein (A), (B), and (C) are present in mass fractions relative to each other such that

Lynch et al. teach that the amphiphile (A) can be phosphatidylcholine ([0050]) and the active (D) can be insulin ([0066]). Lynch et al. teach addition of skin moisturizers thus implying topical skin application ([0066]).

Patel et al. teach a pharmaceutical composition for the topical/transdermal delivery of therapeutic agents comprised of at least one hydrophobic and at least one hydrophilic surfactant as well as solubilizers and mixtures of solubilizers. (Column 25, lines 15-19 and lines 52-53). Polyethylene glycols of average molecular weight of about 200 to about 6000, with PEG-400 a preferred solubilizing agent, are disclosed (Column 25, lines 15-63). Patel et al. disclose that the typical amount of solubilizer present in the composition will be in the range of about 1% to about 100% by weight (Column 26, lines 12-14). Patel et al. teach that hydrophobic surfactants can be in the range of about 1% to about 60% by weight of the hydrophilic surfactant (Column 21, lines 30-31). Patel et al. defines a number of hydrophobic surfactants as oils (Column 9, lines 8-13 and Column 10, lines 1-13; and Table 5, for example). The Examiner is interpreting the addition of such hydrophobic surfactants to mean the addition of a lubricant. Patel et al. further disclose the addition of other additives including preservatives (Column 26, lines 16-21). Methyl paraben is one of the most commonly known preservatives and would be immediately envisaged by one of ordinary skill in the art. Petal et al. is relied upon for teaching the addition of polyethylene glycols to the composition.

Hansen et al. teach a method of making an insulin composition by dissolving semi-synthetic human insulin in 100 ml of 0.02 N HCl and preparing a carrier comprising dioctanoyl, L-alpha-phosphatidylcholine dissolved in distilled water. The carrier was added to the insulin solution and diluted to 1000 ml with water and produced a product with a stability factor of 65 (Columns 7-8, example 22, for example).

Chaiyawat et al. teach cosmetic compositions comprised of silicone fluids of low viscosity, less than 100 cSt at 25 °C, which exist as fluids at or near room temperature (Column

10, lines 48-59). The lubricious silicone fluids include polydimethylsiloxane polymers (dimethicone) (Column 10, lines 60-67 and Column 11, lines 1-4). Furthermore, Chaiyawat et al. teach that such compositions are suitable as hormone carriers (Column 12, lines 35-38 and 66) as well as drug delivery systems for topical administration of medicinal compositions to the skin (Column 12, lines 55-57). Chaiyawat et al. is relied upon for the teaching of adding polydimethylsiloxane lubricants to the composition.

Brieva et al. teach cosmetic compositions comprised of non-volatile silicones, such as Dow 190 (a surfactant), for improved long lasting adherence to the skin of cosmetics (Column 1, lines 4-42; Column 3, lines 53-65). Brieva et al. is relied upon for teaching the addition of Dow 190 surfactant to the composition.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. Amselen et al. or Lynch et al. do not expressly disclose a method of formulating an insulin composition comprising a phosphatidylcholine component comprising 45% w/w phosphatidylcholine, 50% w/w polyglycol E200 and 5% polyglycol E400.

2. Amselen et al. or Lynch et al. do not expressly disclose a method of formulating an insulin composition comprising 53.25% w/w phosphatidylcholine component, 1.00% w/w siloxylated polyether, 1.00% w/w polydimethylsiloxane, and 0.75% w/w methyl paraben and 44% water.

3. Amselen et al. or Lynch et al. do not expressly teach a method of formulating an insulin composition wherein the insulin is human recombinant insulin prepared in 0.01 N HCl at

a concentration of 50 mg/ml or mixing the insulin solution into the carrier for at least one hour and when mixed into said carrier produces an insulin composition having a concentration of 20 mg/ml.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the insulin multilamellar liquid crystalline phosphatidylcholine preparation of Amselen et al. or Lynch et al. with a combination of PEG 200 and PEG 400 as suggested by Patel et al. to produce the instantly claimed invention.

One of ordinary skill in the art would have been motivated to do this because: 1) Amselen et al. and Lynch et al. suggest adding insulin to the multilamellar liquid crystalline carrier and adding other surfactants; and 2) addition of the low molecular weight PEG would enhance the solubility (Patel et al. Column 25, lines 15-18). The specific w/w ratio of the low molecular weight PEGs to the phosphatidylcholine component in the composition and method of mixing is deemed merely a matter of judicious selection and routine optimization of conventional working conditions taught by Amselen et al. and Patel et al., which is well within the purview of one of ordinary skill in the art as suggested by Patel et al. (Column 26, lines 1-2). "Shaving" appears to be nothing more than adding the phosphatidylcholine to the solvent, in the absence of evidence to the contrary, and would be known to one of ordinary skill in the art. The warming of the

components and the choice of 40 C is merely a matter of judicious selection by one of ordinary skill in the art.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of making the carrier composition of Amselen et al. or Lynch et al. to include lubricious silicone fluids, as suggested by Chaiyawat et al., and siloxylated polyethers such DOW 190, as suggested by Brieva et al., and preservatives as suggested by Hansen et al., and produce the instantly claimed invention.

One of ordinary skill in the art would have been motivated to do this because: 1) Amselen et al. and Lynch et al. teach and suggest topical administration to the skin; and 2) Chaiyawat et al. disclose that the addition of such emollients improves the appearance of the skin, reduces flaking and tends to remain on the surface of the skin (Column 10, lines 60-66). Therefore, by adding silicone fluids not only are the aesthetics of the carrier compound improved from a patient standpoint but also the drug delivery capabilities. One of ordinary skill in the art would have been motivated to add DOW 190 because it would have been desirable to increase the adherence of the drug carrier to the skin for optimal drug delivery (Brieva et al. Column 1, lines 41-42). Hansen et al. teach adding preservatives such as methyl p-hydroxybenzoate (methyl paraben) to the insulin composition, which can be prepared separately and added later to the insulin solution (column 4, lines 11-46). With respect to claims 5, 15 and 16, the selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results (In re Burhans, 69 USPQ 330; CCPA 1946) - see, e.g., MPEP 2144.04 (d).

3. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform a method wherein the insulin is human recombinant insulin

prepared in 0.01 N HCl at a concentration of 50 mg/ml or mixing the insulin solution into the carrier for at least one hour and when mixed into said carrier produces an insulin composition having a concentration of 20 mg/ml.

One of ordinary skill in the art would have been motivated to do this because Hansen et al. teaches preparing semi-synthetic human insulin in diluted hydrochloric acid. It is the Examiner's position that semi-synthetic human insulin renders obvious human recombinant insulin to one of ordinary skill in the art. It is the Examiner's position that an acid concentration of 0.01N HCl or an insulin concentration of 50 mg/mL or a final concentration of 20 mg/mL after mixing for at least one hour is merely routine optimization of the composition by one of ordinary skill in the art, in the absence of evidence to the contrary.

Summary: The art teaches preparation of liquid crystalline multilamellar phosphatidylcholine as a carrier for proteins and peptides such as insulin. The art teaches numerous surfactants and lubricants such as polydimethylsiloxane and siloxylated polyethers and solvents/cosolvents such as polyglycols of various molecular weights for use in drug delivery and cosmetic applications. The order of mixing the ingredients is obvious in the absence of unexpected results. Here, it is expected to produce an insulin composition with a non-liposome multilamellar crystal non-polar phosphatidylcholine carrier that is stabilized at room temperature.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant asserts that the carrier of Amselem is simply a liposome. The Examiner cannot agree. In column 13, Table 1, Amselem points out the major differences between a oil-in-water emulsion, a typical liposome and an emulsome. Clearly the invention of Amselem is not a liposome.

Applicant asserts that the particles of Amselem are not multi-lamellar. The Examiner cannot agree. Amselem teaches that one, two or many bilayers or envelopes of phosphoilipid molecules are believed to form around the particles (column 6, lines 50-64; column 13, lines 26-28; column 14, lines 14-20 and claim 1).

Applicant asserts that while Amselen does teach that unnatural surfactants can be added "preferably less than 0.1%" the instant invention comprises up to 55% of the carrier which is made up of ***polar*** polyethylene glycols. However, claim 1 does not recite 55% of the carrier which is made up of ***polar*** polyethylene glycols and Amselen clearly indicates that numerous other synthetic molecules can be used in the invention including a ***polar*** polyoxyethylated one (column 7, lines 63-66).

Applicant asserts that the combination of insulin or polyethylene glycols with the teachings of Amselen would not arrive at the instant invention. The Examiner cannot agree. The Examiner cannot agree. Amselen clearly teaches that both water-insoluble and water soluble actives can be incorporated into the emulsomes (column 8, line 58 through column 9, line 17) as well as adding unnatural surfactants as explained above. The reference of Lynch et al. is relied upon as explained above.

Applicant's arguments are not persuasive and the rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (6:15 am-3:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ernst V Arnold
Examiner
AU 1616

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616